

Evaluation of the drugs' regimens during Ramadan, in Sudan: Patients' prospective

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ABSTRACT

Introduction: The aim of the study was to identify the status of therapeutic regimens administration in Sudan during Ramadan month among patients observing the fast of the holy month. **Methods:** A cross-sectional, study was conducted at public teaching hospitals on patients receiving drug prescriptions and committed to fasting. Patients were interviewed using predesigned questionnaires. They were personally interviewed with regards to their drugs use; regimens; and effectiveness of the drugs. Statistical evaluation was performed with statistical tool (SPSS) package for social science. Data were analyzed by means of the Chi-square Test to compare the differences for various results. The differences were significant at $p \leq 0.05$. **Results:** Two hundred patients participated in the study successfully. An excess of 85 % of the patients continued their daytime- fasting following physician counselling. Enteral administration prevailed, and so did BID regimens. Almost all took nocturnal doses. The drugs' effectiveness in 71% of the adults was not affected by fasting. Seventy three percent of the adults were facing difficulties with their drugs. The majority of cases were patients with upper respiratory tract infections (25.5%). Thirty one percent of the patients used antibiotics. **Conclusion:** Findings are consistent with estimations elsewhere. Regimens were tailored to fit the break-fasting hours. A vista is open for clinical trials on the impact of daytime-fasting on the pharmacodynamic and pharmacokinetic behavior of essential drugs.

Keywords: Sudan, Ramadan, daytime- fasting, intermittent fasting.

1. INTRODUCTION**Ramadan in Islam**

The Islamic Hijra calendar is a lunar calendar. Ramadan is the 9th of its 12 months, each of which consists of 29 to 30 days depending on the birth of the new moon. The Gregorian dates of Ramadan slides by about 10- 12 days earlier every year, and so does each of the other months of the Hijra calendar (Fereidoun et al., 2002). Daily daytime fasting all through the month is obligatory to all Muslim adults (Fereidoun et al., 2002). Fasting begins at dawn and ends with sunset (Aadil et al., 2004), it can last up to 18 hours according to the geographic location and season, Islam recommends that fasting Muslims

eat a meal before dawn (Aadil et al., 2004). Fasting Muslims abstain from food, liquids, tobacco, sexual activity, and oral medications from sunrise to sunset (Bashir et al., 2002; Jaber et al., 2014; Kerry et al., 2014). Some routes of drug administration do not nullify fasting, e.g., eye or ear drops, topical application onto the skin, sublingual nitroglycerin tablets, and drugs through injection into the skin, muscle, or veins (except for intravenous feeding) (Jaber et al., 2014). Oxygen and anaesthetic gases, vaginal administration of pessaries; medicalovules; and/or use of oral sprays, mouthwash, or gargle (provided nothing is swallowed into the stomach), nose sprays and inhalers, anal injections, and surgery involving general anaesthesia do not nullify fasting (Recommendations of the Ninth Fiqh Medical Seminar, 1997). Evenings and nights of Ramadan witness the consumption of two to three meals; the first after sunset (Iftar); the second might be taken around three hours later; the last, recommended, meal shortly before dawn (Sahor) (Aadil et al., 2004).

Importance of Fasting to Muslims

Fasting in Islam is considered as a means of practicing self-control (Leiper, 2003); a way of experiencing what hunger is all about; sympathizing with the poor and of thanking god for everything received in life (Ahmad et al., 2012). Although the sick is exempt from fasting, many continue to fast and therefore abstain from ingestion of food, water, and oral medications and intravenous nutritional fluids (John et al., 2010). It has been reported that the lesser we eat, the body uses the stored fats and detoxify, thereby consuming more fats and cholesterol, which reduces the risk of heart blockage and high glucose and cholesterol levels (Ahmad et al., 2012). Fasting increases metabolic process in the body (John et al., 2010).

License not to fast

Fasting is obligatory for adult Muslims, but some have license not to fast. These include travelers, pregnant; breast feeding; and menstruating ladies, and those who cannot tolerate fasting including patients not able to fast like diabetics; those with renal conditions; and others according to physicians' decision (Suha et al., 2010; Jaber et al., 2014); as mentioned in the Holy Quran: *[Ramadan is the month in which the Quran was revealed. Guidance for humanity, and clear portents of guidance, and the Criterion. Whoever of you witnesses the month, shall fast it. But whoever is sick, or on a journey, then a number of other days. God desires ease for you, and does not desire hardship for you, that you may complete the number, and celebrate God for having guided you, so that you may be thankful]*, (The Holy Quran).

Studies and doses determinations

It has previously been reported that 58% of patients changed their dosing schedule while observing the fast of Ramadan; less than a half abandoned their treatments; and about 20% took their medication in an OD dose (Aslam et al., 2010). Another survey of 325 hospital- outpatients reported the observation that an excess of 64% of the patients shifted to a dosage schedule that fits Ramadan fasting; and that 18% shifted to OD dosage forms (Aslam et al., 1986).

Scope of the study

A challenge is to tailor the dosing regimen to fit the tightly short time of intake allowance; another is to follow dosing guidelines such as those issued to protect antimicrobials against bacterial resistance. This study has been conducted with a view to evaluate drug administration to daytime-fasting individuals, in Ramadan, and the relationship between fasting and the effectiveness of drugs.

Rational of the study

Despite their exemption, by the provisions of Islam, Muslim patients insist on observing the fast of the holy month of Raman. The fast may extend up to 16- 18 hours depending on the season or the geographic location. The impact of this on the patients and their therapeutic protocols is largely unreported, especially in Sudan. The study aimed to identify the status of therapeutic regimens administration in Ramadan month among Sudanese patients.

Objectives

To assess the status of drug use and its consequences in patients observing the fast of Raman

To try to design or predict the suitable regimens to be used under the above mentioned condition

2. METHODS

Study design and area

A cross- sectional study was conducted on patient's administrated drugs, teaching hospitals in Sudan, while adherent to day time-fasting of Ramadan. The study is part of a project launched 2018.

Study population

Patients afflicted with diseases in Ramadan.

Inclusion criteria: All patients taking drugs while committed to daytime- fasting in Ramadan.

Sample size estimation

The formula: $N=PQZ^2/d^2$ was used to calculate the sample size, where N=sample size; p=prevalence factor; Q=1-p; Z=constant 95% occurrence 1.96; d=desired margin.

The formula had suggested that N=384, from this suggested number of participants only 200 patients were included.

Data collection

A- Semi-structured questionnaire

Patients were interviewed, by investigators, through a predesigned questionnaire that contains items that are directly related to disease and drugs' regimens administrated under the condition of focus.

B- Interviews

Patients were interviewed, by investigators, with regards to their drugs' use while daytime- fasting in Ramadan, including the drugs used; regimens used; and effectiveness of the drugs. They were asked further questions regarding the use of popular drugs such as antibiotics, anti-hypertensives, antivirals and self- administered medications.

Data analysis

Statistical evaluation was performed with SPSS computer program Ver.16 Release 16.0.0 (Sept.13, 2007), copy right (c) SPSS INC. USA. Data analysis was conducted by means of the Chi-square Test to compare the differences for various results. The differences were considered to be significant at $p \leq 0.05$.

3. RESULTS

Population characteristics

Two hundred patients successfully participated in the study. Their random distribution included 67.5% adults aged 16-40 years; 29.5% above 41 years old and 0.03% children below 15 years. Females represented 64.5% of the selected sample (Table 1).

Table 1 Population, n=200, characteristics of patients under drugs' treatment and committed to daytime- fasting in the holy month of Ramadan.

Pattern	Frequency	Percentage
1. Age (years)		
Children (0-15)	6	0.03
Adults (16-40)	135	67.5
Elderly (more than 40)	59	29.5
2. Gender		
Male	71	35.5
Female	129	64.5

Administration of drugs

Eighty six percent of the female, and 84.5% of male, patients continued their daytime- fasting following physician counselling. Enteral administration prevailed, and so did BID regimens (38% of females and 47.9% of males); 96.9% of the females and 100% of the males took nocturnal doses (Table 2).

Table 2 Response to questions, of patients under drugs' treatment and committed to daytime- fasting in the holy month of Ramadan, regarding the administration of drugs n=200.

Pattern	Male, n=71 Frequency (%)	Female, n=129 Frequency (%)
1. Physician's decision		
Fasting allowed	61(86)	109(84.5)
Fasting prohibited	10(14)	20(15.5)
2. Route of drug administration		
Parenteral routes	1(0.01)	4(0.03)
Enteral routes	60(85)	105(81.4)
3. Dose regimen		
OD	17(23.9)	31(24)
BID	34(47.9)	49(38)
Morethan two doses	10(14.1)	29(22.5)
4. Dosing schedule		
Daytime dosing	0(00)	3(0.02)
Night dosing	71(100)	125(96.9)
Both	0(00)	1(0.77)

Effectiveness of medications

The drug effectiveness in 53.3% of the adults, 61% of elderly and 50% of children was not affected by fasting. An excess of seventy five percent of the adults, 78% of the elderly and 75% of the children were comfortable with their drug schedule. An excess of eighty percent of the adults, 78% of the elderly and 75% of the children were facing difficulties with their drugs. These results are presented in table 3.

Table 3 Response to questions, of patients under drugs' treatment and committed to daytime- fasting in the holy month of Ramadan, regarding the effectiveness of their medications n=200.

Question	Children n=4 Frequency (%)	Adults n=137 Frequency (%)	Elderly n=59 Frequency (%)
Effect of fasting on drug effectiveness			
No effects	2(50)	73(53.3)	36(61)
Increased effectiveness	1(25)	33(24)	13(22)
Decrease effectiveness	1(25)	31(22.6)	10(16.9)
Feeling about regimen schedule			
Comfortable	3(75)	103(75.2)	46(78)
Not comfortable	1(25)	34(24.8)	13(22)
Facing difficulties?			
Yes	3(75)	110(80.3)	46(78)
No	1(25)	27(19.7)	13(22)

Diseases' and drugs' status

The majority of cases, in the present investigation, were patients with upper respiratory tract infections (URTI), or gastrointestinal tract (GIT) diseases (25.5% for each). Blood diseases constituted up to 22.5%, musclo- skeletal diseases affected 15% of the patients, urinary tract infections (UTI) affected 7.5% of the patients and central nervous system (CNS) conditions mounted up to 4% of the patients. Thirty one percent of the patients used antibiotics and 26% used non- steroidal anti-inflammatory drugs (NSAIDs); 21.18% used GIT drugs; 7.65% used antihypertensive medications; 6.47% used antivirals; 3.53% used antidiabetic treatments; 2.94% used antifungals. These results are presented in Figs. 1 and 2.

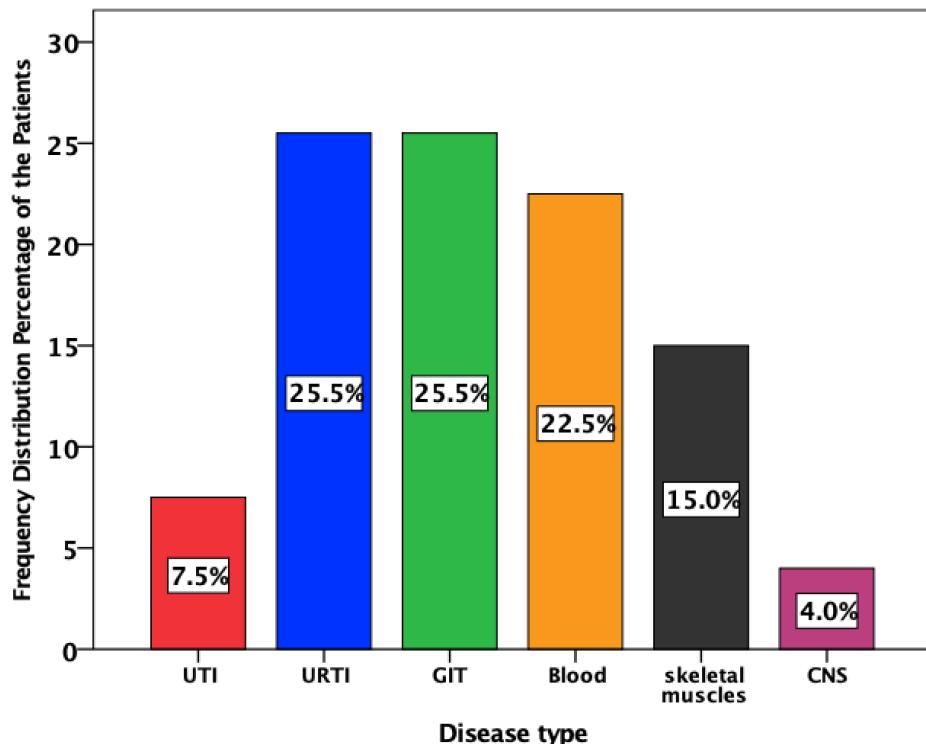


Figure 1 Diseases' statuses of patients under drugs' treatment and committed to daytime- fasting in Ramadan. Red color represents urinary tract infection; blue color represents upper respiratory tract infection; green color stands for GIT conditions; orange color stands for blood diseases; black color stands for musclo-skeletal diseases; and pink color represents central nervous system conditions.

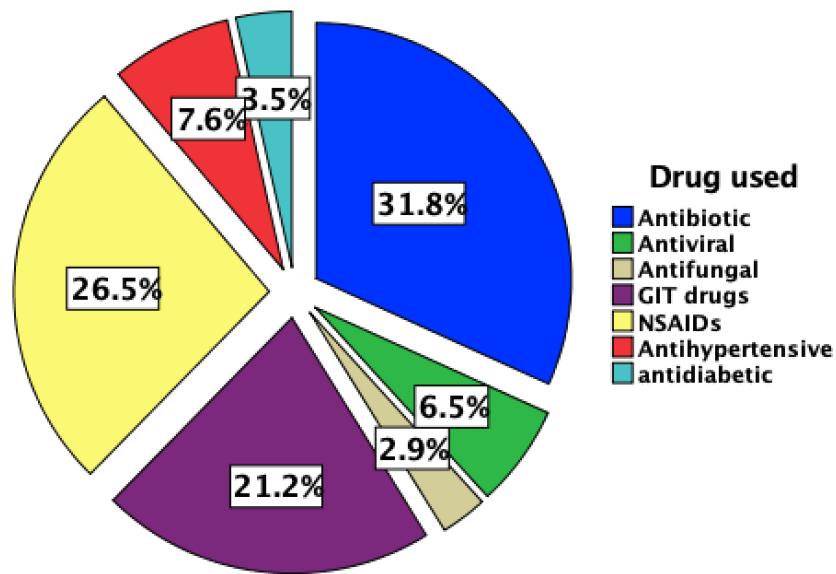


Figure 2 Status of drugs use of by patients under treatment and committed to daytime- Ramadan fasting. Red color represents antibiotics; black color represents antivirals; orange color represents antifungals; green color represents GIT drugs; yellow color represents non- steroidal anti-inflammatory drugs; blue color represents antihypertensive drugs; sky-blue color represents antidiabetic drugs.

Drugs regimen

Forty three percent of the patients took their medication on a BID schedule; 29% used an OD schedule; 27.06% used a TID schedule. All these doses are taken between the breakfast meals (Iftar meal), at sunset and before sunrise (with Sahor meal). Some took a third dose at an additional opted third meal (dinner) in-between. These results are presented in Fig.3.

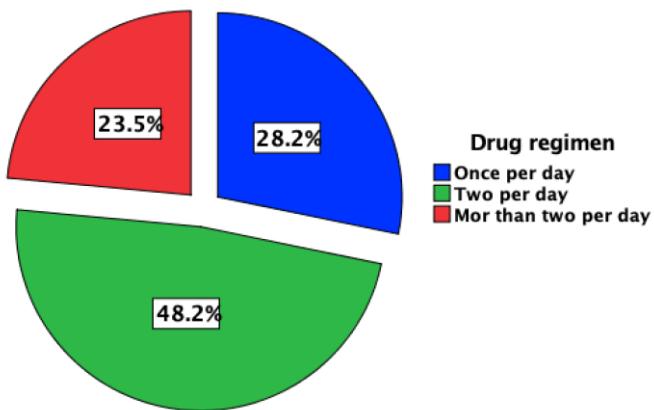


Figure 3 Status of drugs regimens used by patients under treatment and committed to Ramadan's fasting. Black color stands for OD dose after Iftar; orange color stands for TID doses after (Iftar, Dinner, Sahor) each; red color stands for BID doses after (Iftar) and (Sahor) each.

4. DISCUSSION

The patient's sample size (n=200) has been suggested by a computerized formula and gives credibility to the present results compared to previous investigators who noted that their findings are limited by the small sample size (n=31) (Al- Wakeel, 2014); and other relatively small size studies (Boobes et al., 2009; Ahmedani et al., 2016; Addad et al., 2014; Aslam et al., 2010). However, the sample size in some relevant studies is consistent with ours (Siaw et al., 2014; Habib et al., 2009). Most patients, in the present investigation, aged above 16 years ($p=0.000$). This is understandable since fasting according to the provisions of Islam is not obligatory to children. Previous investigators had excluded children from a similar study (Aadil et al., 2004). Predominance of the female gender, in the selected sample (64%) ($p=0.000$), cannot be attributed but to randomization rather than to a natural community phenomenon. However, previous similar studies have noted that approximately 60% of their samples were female (Peeters et al., 2012; Siaw et al., 2014).

It has been determined that 85% and 81.4% of the male and female patients, respectively, used enteral drug formulations, and that about half of this use was in a BID regimen; and that quarter was on an OD regimen, and quarter on a TID regimen. These findings are consistent with several previous findings that patients changed the administration schedule or took all the doses in an OD base (Aslam et al., 2010); patients change the dosing time, route of administration or dosing of drugs sometimes without taking medical advice (Aadil et al., 2004); and the determination that, in some cases, the patient adjustments were simplistic such as skipping a midday dose (Almansour et al., 2017); and that 325 patients changed their drug regimens during Ramadan wherein 18% took their all their daily drug treatments in a single dose (Aslam et al., 1986); and the observation that HIV- AIDS patients safely advanced morning and delayed evening doses thereby prolonging dosing intervals of anti-retroviral therapy (Habib et al., 2009). However, other reports raised concern about regimen alteration and their safety, with the fast, and drug- drug- food interactions (Aadil et al., 2004; Aslam et al., 1986; Hamaguchi et al., 1993; Wilder et al., 2001; Jaber et al., 2014).

These recommended that utmost care should be practiced with the ingestion of drugs that must be administered against an empty stomach (Aadil et al., 2004). Another warned of the significant impact of the alterations to lifestyle, and the dosing schedule, on valproic acid pharmacokinetics (Aadil et al., 2000). It has, presently, been estimated that 84.5% of the female, and 86% of male, patients continued their daytime- fasting following physician counselling. This estimation is consistent with a global observation that patients, with chronic or trivial conditions, insist on observing the fast of Ramadan. It has been observed that patients suffering from minor ailments usually do not have any problems when fasting; and that the majority of physicians advised their patients to fast; and that in an instance when 138 patients were advised by their physicians not to fast, 91 tried to fast and complications occurred in 61 cases (Peeters et al., 2012); and that although people with diabetes may be exempted from fasting, a large proportion still choose to fast (Aadil et al., 2004; Jaber et al., 2014).

A systematic review endorsed Ramadan fasting by diabetic patients not excluding type 1 diabetes mellitus (Alabood et al., 2017). Others reported safety Ramadan fasting for patients with renal grafts whose clinical parameters are normal for an excess of a year (Boobes et al., 2009). It has also been estimated that fourteen-hour fasting for one month was tolerated by chronic kidney disease and hemodialysis patients; although there were considerable changes among hemodialysis patients in some of the blood chemistry variables, nothing serious occurred (Al- Wakeel, 2014). It also is reported that hunger- associated catecholamine inhibition, reduced venous return and decreased sympathetic tone led to better control of hypertension and cardiac disease (Al

Suwaidi et al., 2004); and that Ramadan fasting in stable cardiac patients has no effect on their clinical status (Khafaji et al., 2012). These observations are in general agreement with the previous estimations that 50 million Muslims diabetic patients fast in Ramadan each year, throughout the world (Al-Arouj et al., 2010); and/or the estimation that approximately 116 million Muslims with T2DM fast each year during Ramadan (Hassanein et al., 2017); and the estimation that 79% of type 2 and 43% of type 1 diabetes, out of 12,243 diabetes patients in 13 Muslim countries, fast during Ramadan (Salti et al., 2004).

Most patients (80%) in an earlier study considered participation in Ramadan as (very) important despite their awareness of the exemption from fasting for chronically ill, some patients opted against the medical advice not to fast (Peeters et al., 2012). Most observers choose to fast without informing their doctors and thereby endangering their health (Patel et al., 2015). These risks have been shown to include significant, Ramadan- fasting- associated, decrease of clopidogrel efficacy among diabetic individuals where in there is significantly increased platelet reactivity that persisted 1 month later (Bouida et al., 2017). A European study found that 30%, 51% and 76% patients fasted in Belgium, France, and Muslim countries respectively (Peeters et al., 2012). The present observations by the patients that the effectiveness of drugs, including extensively used drugs, is not affected, ($p=0.001$), are in partial agreement with an earlier report that the qualitative criteria of meals taken during the fast-breaking could have positive influence on the absorption of some drugs (Aslam et al., 1986); and that research on hypotensive medications report no significant reductions in their efficacy from either the life style, or administration schedule, changes in Ramadan (Habbal et al., 1998; Perk et al., 2001); and that Ramadan fasting poses no impact on the effectiveness/ safety of long term oral anticoagulant treatments (Saour et al., 1989).

However, these observations contradict previous findings that derangements of circadian biochemical, physiological, and behavioral rhythms generate variabilities in the efficacy and toxicity of many drugs linked to their time of administration; also, that the accurate distribution of drugs is deranged pertaining to those taken in 2 doses (Aadil et al., 2004); and that in one instance intensive care unit admission has been necessitated by complications due to skipping of medications in Ramadan by patients with chronic reversible respiratory disease (Wheatly et al., 1993); and that there is an impact of fasting on the pharmacokinetics and side effects of theophylline, extended release preparation, taken twice a day (Daghfous et al., 1994); and that in patients with adrenal insufficiency, fasting can cause complications especially if the level of knowledge about the disease is low (Chihaoui et al., 2017); and that there is a relationship between INR fluctuations in patients under acenocoumarol treatment and their observation of Ramadan fasting (Addad et al., 2014).

The present finding that most patients were facing difficulties with their drug regimens, ($p=0.000$), is nothing but expected due to the short time available for oral intake from sunset to dawn. This finding agrees with a report that, intake of drugs, particularly those with multiple doses, is not easy due to time limitation (Tazi et al., 2008). It has been indicated that lest therapeutic problems ensue during Ramadan, dosing ought to be modified by administering slow- release or chronotherapeutic formulations. Otherwise, longer half-life of elimination medicines should be indicated, and that surveys intended to elucidate the therapeutic problems should focus on chronic diseases' medications, particularly medications with limited by narrow therapeutic windows (Aadil et al., 2004). It has been recommended that for trivial infectious or inflammatory conditions requiring treatment, medications with single-daily dosing should be indicated (Tazi et al., 2008).

5. CONCLUSION AND RECOMMENDATION

The status of therapeutic regimens administration during Ramadan month among fasting, Sudanese patients has been estimated. Findings are consistent with estimations elsewhere in the world. Regimens were tailored to fit the break- fasting hours. Change has not included the therapeutic agents themselves.

We recommend the conduction of clinical trials on the impact of daytime- fasting on the pharmacodynamic and pharmacokinetic behavior of essential drugs.

Contribution of the authors to the study

Dr. Aimun AE. Ahmed: Established the study design and supervised it throughout its conduction.

Dr, Maha Jalal: Conducted most of the field work and did the statistical analysis.

Dr. Salah Eldin Abdel Hag Abdel Haleem: Shared in the supervision and did the editing.

Author Disclosure Statement

The authors have no competitive financial interests to disclose.

Ethical Approval

The research proposal was approved by the department of Pharmacology and Toxicology, Africa international University, while written informed consent was obtained from each participant prior collecting the data. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Based on an official letter of approval from the Planning and Training Administration, General Directorate of Medicine, Khartoum State Ministry of Health (No. MH/ KHS/ GDM/PTA/ D/01), the ethics committees of the hospitals approved the study. This article does not contain any studies with animals performed by any of the authors.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Data and materials availability

All data associated with this study are present in the paper.

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